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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,705	09/18/2003	C. Anthony Altar	03235/100M087-US2	5502

7278 7590 01/25/2006

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EXAMINER	
STANDLEY, STEVEN H	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,705	ALTAR ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/26/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *8-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, directed to claims 1-7, and SEQ ID NO: 145, and new claims 30-36 in the reply filed on 10/26/05 is acknowledged. The traversal is on the ground(s) that all the claims are directed to one inventive concept. This is not found persuasive because although the inventions might be conceptually related, U.S. restriction practice does not rely on unity of invention as the decisive means for determining restriction practice. Instead, as set forth in the requirement for restriction of 7/26/05, the claims have been restricted on the basis that they represent multiple distinct inventions that measure mRNA levels of patentably distinct genes and that examination of more than one invention would be burdensome upon the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-7 and 30-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a complex method of identifying compounds to treat "a [generic] neuropsychiatric" disorder by contacting "a [generic] cell" with a test compound, measuring expression levels of "signature genes" defined as those genes "differentially expressed" in response to "electroconvulsive seizure [ECS]". It is complex because it identifies a diversity of genes involved in different cellular processes as "differentially expressed," either singularly or in an ensemble as an indicator(s) of the therapeutic efficacy of any compound for the treatment of any neuropsychiatric disorder.

The prior art does not support a relationship between differential expression of "signature genes" with ECS treatment and therapeutic efficacy of a molecule that treats a neuropsyciatric illness. For instance, Cox-2, the 'signature gene' exhibiting the greatest change and the highest algorithm score with ECS (see appendix 8.3), is actually down-regulated with chronic lithium treatment (see Bosetti et al., 2002), in contrast to the findings and hypothesis of the instant specification. Therefore, lithium would not be identified as a therapeutic in the treatment of bipolar illness using the

instant Cox-2 expression level as a measure of therapeutic efficacy. Therefore it is also unpredictable as to whether the assay would identify compounds that are therapeutic, since lithium is a well-known treatment for bipolar illness.

While it is possible that some molecules support the positive changes ascribed to ECS, the art does not teach which, if any, or how many (if more than one) mRNA transcripts are related to such changes. As Newton et al. (2003) suggest in a post-filing date manuscript describing microarray analysis of brain tissue in animals having undergone ECS, "Future studies will be required to assess the clinical relevance of these results by comparing the time course for the regulation of identified genes with behavioral effects of ECS. Research focused on manipulating these cascades at different levels using specific inhibitors or gene delivery techniques and assessing the functional and behavioral outcomes will help elucidate the contributions of individual molecules and their signaling cascades in the action of anti-depressant treatment [Newton et al., 2003, summary on pate 10849]." In short, Newton et al suggests the instant invention is merely an invitation for further experimentation.

The specification does not teach any nexus between the increased expression of the disclosed genes and any therapeutic effects related to neuropsychiatric disorders. There is no specific guidance as to whether the change in expression of one, two, three, ten, or one hundred and fifty four genes is sufficient to indicate that a compound is therapeutic, nor to what degree of overexpression of what mRNAs is sufficient to indicate the compound is therapeutic. There are no working examples wherein the invention is demonstrated to identify any compounds.

As indicated above by Newton et al., as of 2003, significant future study would be required to identify the relationship between "differentially expressed genes" and their therapeutic value, even as a just a measure of therapeutic efficacy. Thus, the quantity of research required to enable one of skill in the art to use the instant invention would be extensive and undue.

Therefore, given the complex nature of the invention, the contrasting findings and the lack of support in the prior art, the lack of any specific guidance as to what really indicates a molecule would be therapeutic, and the quantity of experimentation to determine what *does* indicate a molecule is therapeutic, one skilled in the art could not use the invention without undue experimentation.

3. Claims 1-7, and 30-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, the definition for "signature genes," disclosed in the summary of invention is "nucleic acids that are differentially expressed in patients undergoing electroconvulsive therapy." The sum of these genes that are differentially expressed are not known or taught in the specification. While the Tables define approximately 150 genes that are differentially expressed in rats in response to ECS, there are an

estimated 30,000 genes in the human genome and it has been estimated that as many as 40% of all genes in the human genome have splice variations witch confer unique functional properties on the polypeptide sequence encoded (Modrek et al, January, 2002; see Alternative splice frequency on page 13, and Functional Impact, on page 14). These splice variations are encoded by unique sequences of nucleic acid which are either included or not included in the final mRNA form, and it the specification does not indicate which splice variations are measured or which ones change in response to ECS. For instance, the NMDA receptor NR1 subunit is listed as one preferred "signature gene," and this receptor has at least 8 know splice variants that confer different properties to the polypeptides, and which are also differentially expressed in the brain (See Laurie et al., 1994). The specification does not teach the region of the mRNA transcript that is probed or the antisense oligonucleotide sequence used. Therefore it is not known what NR1 expression the specification refers to.

Moreover, the claims recite 'signature genes,' and one skilled in the art knows that the gene sequence includes both coding exons, non-coding introns, and 5' and 3' regulatory regions. Neither the art nor the specification teaches the structures of the 'signature genes' recited.

Thus, the claims are to a genus of "signature genes" which are described as genes that are "differentially expressed" with ECS, and of which there could be thousands of unknown and undisclosed genes that are 'differentially expressed,' along with thousands of splice variations in addition which could be differentially expressed but are not described in the specification. Also, the claims do not indicate what

oligonucleotide sequence is being used for hybridization. Therefore, there are no clear structural limitations on what gene product is really being measured, because as many as 40% of the genes have one or more splice variations. Thus, the claims are drawn to a differential expression of a genus of nucleic acids that have no clear structural definition.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. In the instant application, no such distinctions have been made. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of a name.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-7, 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Step (b) of claim 1 recites "determining expression." A skilled artisan does not know by what means or what conditions "determining expression" indicates, since no definition is provided in the specification and "determining expression" may be accomplished by any one of many means. Independent claim 34 is rejected for the same reason. Claims 2-7, and 30-36 are rejected, as they depend from claim 1 or 34.

5. Claims 1-7, and 30-36 are further rejected because it is entirely unclear what constitutes the metes and bounds of "differentially expressed." The term "differentially expressed" in claim 1 is a relative term which renders the claim indefinite. The term "differentially expressed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-7 and 30-33 are rejected for depending from claim 1.

6. Claims 1-7, and 30-36 are further rejected because it is unclear what "comparing the determined expression" of part (C) refers to. Does it refer to the expression level already determined from the specification, or does it refer to the newly determined expression in the presence of a compound. Independent claim 34 is rejected for the same reason. Claims 2-7, and 30-36 are rejected, as they depend from claim 1 or 34.

7. Claims 1-7, and 30-36 are further rejected because it is entirely unclear as to what constitutes "changes in expression of the one or more signature genes consistent with a therapeutic effect indicate[s] the test compound is useful for treating a neuropsychiatric disorder." It is unknown in this case, what the metes and bounds of "a therapeutic effect" are, because the specification describes no specific change in expression of genes that is linked to a therapeutic effect. Further, because it is not known what is "consistent with a therapeutic effect indicate[s] that the test compound is useful for treating the neuropsychiatric disorder" the phrase is given no patentable

weight. Independent claim 34 is rejected for the same reason. Claims 2-7, and 30-36 are rejected, as they depend from claim 1 or 34.

8. Claims 1-7, and 30-36 are further rejected because it is not known what the metes and bounds of "a method for identifying a compound to treat a neuropsychiatric disorder," because it is entirely unclear how the compound can be determined to be therapeutic (i.e., it lacks a clears step wherein the method is accomplished--as described in § 7.). Independent claim 34 is rejected for the same reason. Claims 2-7, and 30-36 are rejected, as they depend from claim 1 or 34.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-7, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakao et al. (1994).

Because they are indefinite, neither the preamble nor the conclusion of claim 1 is given any patentable weight in considering prior art. Nakao et al. teach contacting a rat (which comprises a cell) with a compound (lignocaine) and measuring c-fos (which is a 'signature gene'). Nakao et al compare the expression of c-fos in lignocaine treated animals to control (page 848, table I) and ECS-treated animals (figure 5, compare A with D), and conclude that lignocaine did not produce the same change in the "signature

gene" c-fos that ECS did. Thus, meeting the limitations of claims 1-5. Nakao et al evaluated the sum of c-fos expression (in many regions of the brain; see table 1), which meets the limitations of "evaluating from a value of V," of claim 6. Nakao et al normalize all values by dividing 'positive area/total area' and then express that fraction as a 'percent' which is multiplying by 100, which is reasonably a 'weighting factor,' because '100' represents a coefficient applied to elements of a frequency distribution (in table I, the percentage values in different regions) to represent their importance.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on **(571) 272-0867**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.
1/17/06

LORRAINE SPECTOR
PRIMARY EXAMINER